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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,927	04/09/2007	Axel Niendorf	5151-21PUS	4186

27799 7590 10/05/2011

Cozen O'Connor
277 Park Avenue, 20th floor
NEW YORK, NY 10172

EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
10/05/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,927	NIENDORF ET AL.	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/30/11*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *24-35 and 38-60* is/are pending in the application.

5a) Of the above claim(s) *29,30,33-35,42,43,46,48,52,53 and 55-58* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *24-28,31,32,38-41,44,45,47,49-51,54,59,60* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 30, 2011 has been entered.

2. Claims 24-35 and 38-60 were previously pending, with claims 29, 30, 33-35, 42, 43, 46, 48, 52, 53 and 55-58 withdrawn from consideration. Applicants amended claims 24 and 25. Claims 24-28, 31, 32, 38-41, 44, 45, 47, 49-51, 54, 59 and 60 will be examined.

3. Applicants' amendments did not overcome any of the previously presented rejections for reasons given in the "Response to Arguments" below.

Response to Arguments

4. Applicant's arguments filed March 30, 2011 have been fully considered but they are not persuasive.

Regarding the rejection of claims 24-28, 31, 32, 38-41, 44, 45, 47, 49-51 and 54 under 35 U.S.C. 103(a) as being unpatentable over Adeyinka et al. and Sgroi et al., Applicants argue the following:

i) "Independent claim 1 has been amended to recite: "during clinical diagnostics", "two of the prepared sections are subjected to the histological/cytological examination, and the two of the prepared sections are selected so that the at least another one of the prepared sections subjected to the non-morphological analytical testing is from a portion of the tissue sample that was between the two of the prepared sections in situ."

As stated in MPEP §2143, to reject a claim based on a combination of references, Office personnel must articulate the following:

(1) a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;

(2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely performs the same function as it does separately;

(3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and

(4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

At least the first, second and third requirements are not met by the Examiner's rejection because (1) Adeyinka and Sgroi are directed only to methods for conventional basic research, and not to methods for use during clinical diagnostics and (2) Sgroi fails to disclose "two of the prepared sections are subjected to the histological/cytological examination, and the two of the prepared sections are selected so that the at least another one of the prepared sections subjected to the non-morphological analytical testing is from a portion of the tissue sample that was between the two of the prepared sections in situ", as expressly recited by independent claim 24."

ii) "As stated in MPEP 2143.01, the mere fact that references can be combined or modified does not render the resultant combination obvious unless **>the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.,* 550 U.S.__, __, 82 USPQ2d 1385, 1396 (2007). The mere existence adjacent immunohistochemical staining of tissue sections adjacent to slices used for LCM in Sgroi does not mean that such a process would be obvious to use in the method of Adeyinka, or that even if Adeyinka and Sgroi were to be combined a process resulting from the combination thereof would be obvious to use during clinical diagnostics. MPEP 2143.01 further states that if proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon,* 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). As will be described in more detail below, the processes of Adeyinka and Sgroi would not and could not be used during clinical diagnostics because Adeyinka and Sgroi are directed only to methods for conventional basic research, and not to methods for use during clinical diagnostics."

iii) "Adeyinka is directed only to conventional basic research. Adeyinka discloses that the human DCIS tumor samples are obtained from a tumor bank for the method described therein. (See p. 3789, Materials and Methods, Human Breast Tumor Samples, first paragraph). Adeyinka does not disclose, teach or suggest any method performed during clinical diagnostics. Moreover, Adeyinka's process for basic research requires steps for tissue microdissection, RNA extraction and microarray cDNA membranes. Adeyinka's process is thus completely unconcerned and incompatible with clinical diagnostics.

Sgroi does disclose that all tissue used for his study is obtained from a modified radical mastectomy specimen from a single patient. (See p. 5656, col. 2, Materials and Methods, LCM, first

paragraph). However, Sgroi is directed only to conventional basic research, i.e., detailed molecular genetic analysis of patient tissues. (See the Abstract of Sgroi). That is, Sgroi's method of analysis comprises steps for RNA extraction, RNA labeling and Hybridization and Immunoperoxisdase staining and is therefore available only for conventional basic research, and not for more time-sensitive clinical diagnostics. Indeed, Sgroi process is completely unconcerned and incompatible with clinical diagnostics."

iv) "Furthermore, one skilled in the art at the time of the present invention would not have combined the teachings of Adeyinka and Sgroi, which relate to only conventional basic research, to achieve the present invention because they are completely unconcerned with a clinical diagnostics situation in which a surgeon takes a tumor sample from a patient during a clinical operation, and a pathologist immediately slices the sample into different sections to give direct, immediate feedback to the surgeon with respect to whether the sample comprises tumor tissue so the surgeon can make a determination as to how to proceed in the clinical operation. Moreover, as noted above, Adeyinka and Sgroi's processes are unsuited for performance during clinical diagnostics because they are not adaptable for the time-sensitive nature and local clinical restrictions of clinical diagnostics. The skilled artisan therefore would not and could not have combined the basic research methods of Adeyinka and Sgroi to be performed during clinical diagnostics. Indeed, a pathologist conventionally takes a number of slices and investigates them histologically, which means that potential information with respect to a molecular signature is not considered during conventional clinical diagnostics even though such information could be extremely helpful for patient specific therapy. In contrast, Applicants' claimed invention does not change standard clinical protocol by performing "during clinical diagnostics" a method wherein "two of the prepared sections are subjected to the histological/cytological examination, and the two of the prepared sections are

selected so that the at least another one of the prepared sections subjected to the non-morphological analytical testing is from a portion of the tissue sample that was between the two of the prepared sections in situ".

v) "Adeyinka and Sgroi therefore fail to disclose, teach or suggest "during clinical diagnostics", "two of the prepared sections are subjected to the histological/cytological examination, and the two of the prepared sections are selected so that the at least another one of the prepared sections subjected to the non-morphological analytical testing is from a portion of the tissue sample that was between the two of the prepared sections in situ", as now expressly recited by Applicants' amended claim 24. Erlander is likewise directed only to conventional basic research and, thus, fails to cure the deficiencies of Adeyinka and Sgroi discussed above with respect to independent claim 1.

Regarding the second reason, the Examiner considers Sgroi to disclose the claimed selection of tissue sections for histological/cytological examination and non-morphological analytical testing. However, Sgroi explicitly discloses that the sections for histological/cytological examination are consecutive tissue samples. (See caption for Figs. 3A and 3B on page 5660 of Sgroi). The advantages of taking sections for non-morphological analytical testing that are between sections used for histological/cytological examination are disclosed at paragraphs 52-55 of the published application, and are not merely design choice. The prior art cited by the Examiner thus fails to disclose, teach or suggest "two of the prepared sections are subjected to the histological/cytological examination, and the two of the prepared sections are selected so that the at least another one of the prepared sections subjected to the non- morphological analytical

testing is from a portion of the tissue sample that was between the two of the prepared sections in situ", as expressly recited by independent claim 24."

Applicants arguments are not considered to be persuasive. First, the only limitation added to the claims was "during clinical diagnostics". There is no definition of what "clinical diagnostics" means, and no steps specific for "clinical diagnostics" were added. Further, the method steps, whether performed in clinical or research settings are the same, and it is the method steps that are compared to the prior art. Both Adeyinka et al. and Sgroi et al., contrary to Applicants' allegations, dealt with real tumors from clinical patients, and their methods were performed in a clinical setting with a clinical goal of establishing, in case of Adeyinka et al., recurrence of invasive breast tumors, and in case of Sgroi et al., evaluating molecular basis of breast cancer. Whether in a clinical procedure or not, the tumors still need to be sliced and the slices analyzed. Finally, in order to use results of molecular analysis for clinical diagnosis, the basis for such diagnosis needs to be established which is the case in the Adeyinka et al. and Sgroi et al. papers. In conclusion, both references specifically teach and suggest clinical diagnosis.

As to inoperability of the combined teachings of Adeyinka et al. and Sgroi et al., both references teach obtaining slices of frozen sections from breast tumors and both use microdissection to obtain tumor cells for further analysis, except that Adeyinka et al. do not specifically teach how the slices were obtained. Sgroi et al. is used to teach specifically that immunohistochemistry was performed on slices adjacent to the slices used for molecular analysis. Therefore, the way of selecting slices of Sgroi et al. would not make the method of Adeyinka et al. inoperable, since Adeyinka et al. do not teach any specific ways to select slices for examination.

As to the selection of tissue slices, the slices selected would obviously depend on the quality of the tissue block, etc. Applicants did provide any evidence that selecting tissue slices in any particular way provided unexpected results in the performed method.

The rejection is maintained.

Claim Interpretation

5. Applicants defined the term "non-morphological analytical testing" in paragraph [0017] as follows:

"In the discussion which follows, the term "nonmorphological analytical testing" is understood to mean especially molecular-biological analyses."

6. Applicants did not define the term "image processing system", therefore it is interpreted as any device or system used in visualizing samples or cells, such as a microscope, for example.

7. The phrase " wherein the determined at least one of a quantitative fraction of diseased tissue or cells and another morphological aspect is used as a reference quantity on which evaluation of a result of the non-morphological analytical testing is based" is interpreted as any correlation between morphological aspects and results of non-morphological analytical testing, since the term "reference quantity" was not defined.

8. The limitation "wherein in the histological/cytological examination, part of the tissue sample is used to quantify an amount of contaminating, non-diseased cells which are accounted for in the subsequent non-morphological analytical testing" is interpreted as using the quantity of non-diseased cells in any testing used subsequent to the histological/cytological analysis.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 24-28, 31, 32, 38-41, 44, 45, 47, 49-51 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adeyinka et al. (Clin. Cancer Res., vol. 8, pp. 3788-3795, 2002; cited in the previous office action) and Sgroi et al. (Cancer Res., vol. 59, pp. 5656-5661, 1999; cited in the previous office action).

A) Claims 24 and 25 will be considered together in claim 24, since it is a species of claim 25.

Regarding claims 24 and 25, Adeyinka et al. teach a method comprising:

preparing sections from the tissue sample (page 3789, second and third paragraph);

subjecting at least one portion of the sample to a histological/cytological examination (page 3789, third paragraph); and

subjecting at least another portion of the sample to a non-morphological analytical testing (page 3789, paragraphs 4 and 5; page 3790, paragraphs 2-4),

wherein in the histological/cytological examination, at least one of a quantitative fraction of diseased tissue or cells and another morphological aspect of the at least one portion of the sample is

determined by an image processing system (page 3789, second paragraph; since the histological examination is performed using a microscope, as evidenced by Encyclopedia Britannica, Adeyinka et al. inherently teach using an image processing system),

wherein in the histological/cytological examination, part of the tissue sample is used to quantify an amount of contaminating, non-diseased cells which are accounted for in the subsequent non-morphological analytical testing (Adeyinka et al. teach adjusting the levels of mRNA expression by multiplying them by the percentage of ductal cells (page 3790, fifth and sixth paragraphs), and

wherein the determined at least one of a quantitative fraction of diseased tissue or cells and another morphological aspect is used as a reference quantity on which evaluation of a result of the non-morphological analytical testing is based (page 3791, paragraphs 2-4; Table 2; Fig. 2; page 3792, last paragraph; page 3793, paragraphs 1-3).

Since Adeyinka et al. teach using clinical samples with a goal of predicting tumor inasivness and progression (page 3788, first and second paragraph), they inherently teach performing the method steps during clinical diagnostic process.

Regarding claim 26, Adeyinka et al. teach samples obtained by sectioning tissue blocks (page 3789, paragraphs 2-4). Since Applicants did not define "core sampler", any device used to section the tumor is considered to be a "core sampler".

Regarding claims 27 and 28, Adeyinka et al. teach that morphological appearance of the cells is correlated with the expression pattern of the genes (page 3791, paragraphs 2-4; Table 2; Fig. 2; page 3792, last paragraph; page 3793, paragraphs 1-3).

Regarding claims 31 and 32, Adeyinka et al. teach frozen samples (page 3789, second paragraph).

Regarding claims 38 and 39, Adeyinka et al. teach using the results for experimental pathological analysis (page 3791, paragraphs 2-4; Table 2; Fig. 2; page 3792, last paragraph; page 3793, paragraphs 1-3).

Regarding claims 40 and 41, Adeyinka et al. teach detecting biomolecules such as mRNA (page 3789, paragraphs 4 and 5; page 3790, paragraphs 2-4).

Regarding claims 44 and 45, Adeyinka et al. teach using microarrays (page 3790, second paragraph).

Regarding claims 47 and 49, Adeyinka et al. teach amplification (page 3790, third and fourth paragraphs).

Regarding claims 50 and 51, Adeyinka et al. teach staining (page 3789, second paragraph).

Regarding claim 54, Adeyinka et al. teach subjecting cells to additional histological examination (page 3789, third paragraph).

B) Regarding claims 24 and 25, Adeyinka et al. teach preparing the sections for non-morhological analysis from frozen tissue blocks which are mirror-images of formalin-fixed tissue blocks (page 3789, first paragraph), but do not teach using tissue sections adjacent to sections used for non-morphological testing for histological/cytological examination.

C) Sgroi et al. teach analysis of tissue sections from a breast cancer using histology and microarray hybridization (page 5656, paragraphs 3-5; page 5657, paragraphs 1-3). They teach confirmation of the array analysis data by analyzing sections adjacent to the ones used for microarray analysis by immunohistochemistry (page 5657, fifth paragraph; page 5659, last paragraph; page 5660, first paragraph). They also morphologically examined sections corresponding to the LCM sections used for PCR analysis (Fig. 3B).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the additional confirmation method of Sgroi et al. in the method of Adeyinka et al. The motivation to do so is provided by Sgroi et al., who state (page 5659, last paragraph; page 5660, first paragraph):

"As an additional means to confirm our data at the protein level, we performed immunohistochemical analysis of apolipoprotein using tissue sections that were adjacent to those used for laser microdissection. Paralleling the differential expression pattern observed with the cDNA microarray and RTQ-PCR analysis, the invasive cells demonstrated abundant and strong immunoreactivity for apolipoprotein D, whereas the metastatic cells demonstrated rare and weak immunoreactivity (Fig. 3*B*). This result further supports the reliability of our expression data and demonstrates the cellular specificity of the apolipoprotein gene expression. Overall, the RTQ-PCR and immunohistochemistry results support the feasibility of our microarray experimental protocol as a means to assess *in vivo* transcript expression profiles."

12. Claims 59 and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adeyinka et al. (Clin. Cancer Res., vol. 8, pp. 3788-3795, 2002; cited in the previous office action) and Sgroi et al. (Cancer Res., vol. 59, pp. 5656-5661, 1999; cited in the previous office action), as applied to claims 24 and 25 above, and further in view of Erlander et al. (US 2003/0186248 A1; cited in the IDS and in the previous office action).

Claims 59 and 60 are drawn to the methods of claims 24 and 25 used to adjust patient's individualized cancer therapy. Adeyinka et al. teach that products of genes identified using molecular analysis can serve as a basis for assessing the risk of progression of DCIS or providing targets for new therapies (page 3788, last sentence; page 3789, first paragraph).Erlander et al. teach that the results of correlation between histological/cytological features and sensitivity or resistance

to a particular therapeutic agent or treatment, including information regarding the likelihood of success or failure of various treatment regimens for the disease (page 4, [0026]). Therefore, in view of these teachings of Adeyinka et al. and Erlander et al., it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the information regarding treatment outcomes to adjust therapy of individual patients based on their histological and molecular signatures.

13. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka

Primary Examiner
Art Unit 1637

/Teresa E Strzelecka/
Primary Examiner, Art Unit 1637
September 29, 2011